REMARKS

The Office Action mailed August 2, 2005, has been received and carefully reviewed. Applicants acknowledge, with appreciation, the withdrawal of finality of the previous Office mailed March 24, 2005.

The pending claims are claims 1-13. Reconsideration and withdrawal of the rejection of claims 1-13, in view of the following remarks, is respectfully requested.

Rejection under 35 U.S.C. §103

The Examiner indicates that claims 1-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Madison et al., Johnston et al., Clemente et al. and Linde et al.

Applicants note for the record that claims 1-13 are actually "newly rejected" under 35 U.S.C. §103, as Linde et al. is newly cited. The Examiner acknowledges this at page 5 of the instant Office Action, stating that the Examiner has "issued a new rejection citing new art."

In order to establish a *prima facie* case of obviousness, the Examiner must show that there is a motivation to combine the documents (or modify a the teachings of a document) to achieve the claimed invention, with a reasonable expectation of success. Further the references must teach or suggest every element of the claimed invention. It is respectfully submitted that the Examiner has failed to make the requisite showing of a *prima facie* case of obviousness.

Claim 1 recites:

> 1. A method for the production of a polyhydroxyalkanoate (PHA) comprising:
> providing a transgenic yeast cell comprising a first nucleic acid fragment comprising a heterologous nucleotide sequence encoding a PHA polymerase and at least one second nucleic acid fragment comprising a heterologous nucleotide sequence selected from the group consisting of a heterologous nucleotide sequence encoding an acetoacetyl-CoA reductase and a heterologous nucleotide sequence encoding a β-ketothiolase;
> culturing the transgenic yeast cell under anaerobic conditions to cause the production of PHA; and
> isolating the PHA from the yeast cell.

Applicants submit that claim 1, as well as claims 2-13 which are dependent thereon, are nonobvious in view of the cited art at least because the cited art, either alone or in combination, do not teach or suggest culturing the transgenic yeast cell under *anaerobic conditions* to cause the *production of PHA*.

As acknowledged by the Examiner, Madison et al. teach production of a PHA in transformed *S. cerevisiae*, but do not teach a method of producing PHA in transformed yeast *anaerobically*. The Examiner cites new art to show that it is well-known that *S. cerevisiae* is able to grow both aerobically and anaerobically.

Linde et al. is newly cited by the Examiner for the proposition that "gene expression under anaerobic and anaerobic [sic] conditions showed little difference" and concluded that a reasonable expectation of success existed because, in combination with Madison et al., Clemente et al. and Johston et al., "Linde teaches flexibility of expressing genes in anaerobic and aerobic culture conditions."

In response, Applicants respectfully contend that Linde et al. do *not*, particularly with respect to the present invention, suggest such straightforward flexibility. Linde et al. teach that "*[i]n quantitative terms*, the aerobic and anaerobic transcript profiles of *S. cerevisiae* exhibit little difference" (Linde at col. 2, p. 7412; emphasis added). *However*, they also note that a small number of genes exhibited a *greater than 10-fold difference* between aerobic and anaerobic mRNA levels. Notably, this small group includes several genes that the authors state could be directly linked to typical aerobic process, among them genes involved in *β-oxidation*, including PXA1, a transporter involved in translocation of long-chain fatty acids across the peroxisomal membrane, and FOX2, encoding 3-hydroxyacyl coenzyme A epimerase (Linde at col. 2, p. 7412).

Applicants do not dispute that anaerobic cultures of yeast are well known. It is the successful production of PHA under anaerobic conditions that is surprising. As noted at page 15, lines 7-11, of the specification:

> Anaerobic production of PHA in microorganisms is surprising because PHA is typically considered an *aerobic storage material* in microorganism cells. *Moreover, β-oxidation of fatty acids is an aerobic process, and removing oxygen from the system might have been expected to reduce the precursor pool and thereby inhibit PHA production* (emphasis added).

Because it is a process affected by β-oxidation, an aerobic process, PHA production would, according to Linde et al., be *more likely* to be affected by change from aerobic to anaerobic culture conditions (see col. 2, p. 7411). Linde et al. thus actually *teach away from* the present invention by implying that an aerobic process such as fatty acid metabolism (and hence, PHA production) would, if anything, be adversely affected by anaerobic culture conditions. Moreover, not only do Linde et al. fail to support a reasonable expectation of success, but further, in view of Linde's teaching of a drop in transcript levels associated with typical aerobic processes of over 10X, a skilled artisan would *not* be motivated by Linde et al. to combine the references to carry out an aerobic process such as PHA production under anaerobic conditions.

Applicants additionally point out that the specification further states, in connection with a discussion of redox balance in yeast, that maintaining a favorable redox balance plays a critical role in an organism's metabolism (specification at page 20, lines 24-25) and that anaerobic conditions pose a *redox challenge* because the electron transport system is not available to accept electrons (specification at page 20, lines 32-33). In that regard the specification points out the absence in yeast of a transhydrogenase system, which would provide an alternative pathway for reoxidation of NADH (specification at page 21, lines 10-12).

For at least these reasons, it is respectfully submitted that the cited art provides neither a motivation to combine the cited references, nor a reasonable expectation of success in achieving anaerobic production of PHA in yeast, and that the Examiner has failed to establish a *prima facie* case of nonobviousness. Reconsideration and withdrawal of the rejection of claims 1-13 under 35 U.S.C. §103 is, accordingly, kindly requested.

Respectfully submitted for
SRIENC et al.

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

October 27, 2005
Date

By: V A Sandberg
Victoria A. Sandberg
Reg. No. 41,287
Direct Dial (612)305-1226

VAS/skd

CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to: Commissioner for Patents, Mail Stop Amendment, P.O. Box 1450, Alexandria, VA 22313-1450, on this 27th day of October, 2005, at 4:30 pm (Central Time).

By: Sue Dombroske
Name: Sue Dombroske